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COMPLETE SPECIFICATION

Improvements in or relating to Oleaginous Pharmaceutical Compositions

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to therapeutic compositions and more particularly to oleaginous compositions suitable for the treatment of dry skin and related dermatological disorders of the human skin.

The human skin is covered with an oleaginous film of secreted material called sebum. The material serves to protect the skin from damage such as over-wetting, over-drying, and rapid change of temperature. The film also serves as a barrier against the invasion of bacteria and fungi. When the skin is deprived of this protective film, because of either an inability to secrete the material or for reason of an excessive and continuous removal, the human skin dries, hardens, and develops fissure, giving rise to the condition known as dry skin. The various compositions proposed for the alleviation of dry skin have had a variety of disadvantages such as lack of efficacy, cosmetic unacceptability, and the inability to form stable emulsions with water in the absence of a surfactant.

The compositions of the present invention do not have these disadvantages and yet can be prepared in several pharmaceutical forms, e.g., an ointment comprising about 5% to 20% of saturated fatty acids having not less than 12 and not more than 20 carbon atoms, about 10% to 30% of unsaturated fatty acids having not less than 12 and not more than 20 carbon atoms, about 10% to 20% of glyceryl monostearate, about 15% to 25% of a fixed oil, from about 2% to 10% of a wax consisting of esters of a fatty acid having not less than 12 and not more than 20 carbon atoms and a fatty alcohol having not less than 12 and not more than 20 carbon atoms, about 5% to 18% of a fatty alcohol having not less than 12 and not more than 20 carbon atoms, about 2% to 5% of cholesterol, about 3% to 8% of squalene, and about 5% to 15% of petrolatum, liquid petrolatum or mixtures thereof; an oil-in-water emulsion comprising the aforementioned ointment dispersed in water in the proportions of 1 part of ointment to about 1 to 19 parts of water; and a water-in-oil emulsion comprising the aforementioned ointment having water dispersed therein in the proportions of about 85—99 parts ointment to about 1—15 parts of water. Advantageously the composition can also contain glycerin, an anti-oxidant, and anti-bacterial and anti-fungal preservatives.

The compositions of the present invention are useful for therapeutic or prophylactic treatment of the human skin, especially those conditions arising from the absence of sebum. When applied to the skin, the compositions serve to provide an oleaginous film similar to the natural film present on healthy skin. The compositions are also useful vehicles for the topical application of such therapeutic agents as sunscreens, antibiotics, vitamins and anti-inflammatory agents.

Unless otherwise specified, the percentages given in the specification and claims are on a weight to weight (w/w) basis and in the following description of the various oleaginous ingredients, the percentages given relate to the percentage of the oleaginous ingredient in the ointment (non-aqueous) compositions.

The ointment compositions contain both saturated and unsaturated free fatty acids, said fatty acids having not less than 12 and not more than 20 carbon atoms. The saturated fatty acids are present in a concentration of about 5% to 20% with about 10% being the preferred concentration. Stearic and palmitic acids are the preferred saturated acids. The unsaturated acids are present in a concentration of about 10% to 30% with

about 20% being preferred. Oleic and linoleic acids are preferred.

Saturated and unsaturated fatty alcohols having not less than 12 and not more than 20 carbon atoms are present in a concentration of about 5% to 18% with about 12% being preferred. Lauryl, stearyl, cetyl and oleyl alcohols are preferred.

Esters of the aforementioned classes of fatty acids and fatty alcohols are present in a concentration of about 2% to 10% with about 6% being preferred. The esters used can be the naturally occurring waxes such as spermaceti or the prepared esters such as cetyl palmitate and cetyl stearate.

About 15% to 25% of the ointment is a fixed oil, i.e., a fat which is liquid at ordinary temperatures, comprised of mixed di- and triglyceryl esters of higher fatty acids. Fixed oils such as corn oil, expressed almond oil and cottonseed oil can be used. Corn oil is preferred at a concentration of about 25%.

Glyceryl monostearate is present in a concentration of about 10% to 20%, with about 15% preferred. When the ointment is used to form an emulsion, the glyceryl monostearate serves as the emulsifying agent. Other glyceryl mono-esters such as glyceryl monooleate can be used in a concentration up to about 5%. When so used, the esters can be in addition to the glyceryl monostearate or can be used to replace an equivalent amount of the glyceryl monostearate.

The topically acceptable hydrocarbons petrolatum, liquid petrolatum (mineral oil) and mixtures thereof are present in a concentration of from 5% to 15%. By varying the proportions of the liquid and solid petrolatums the consistency of the ointment can be varied.

Squalene in a concentration of about 3% to 8%, with about 5% preferred and cholesterol in a concentration of about 2% to 5%, with about 3% preferred, are also present in the ointments.

Advantageously, additional ingredients can be added to the compositions, especially when in the form of an emulsion. Polyhydric alcohols such as glycerin and propylene glycol are added in a concentration of about 5% and serve as humectants and add to the cosmetic elegance of the emulsion. Antioxidants such as α-tocopherol in a concentration of about 0.01 to 0.1% and preservatives such as methylparaben, propylparaben, n-butyl-p-hydroxybenzoate in a conconcentration of about 0.1% serve to protect compositions during storage.

When the compositions are used as a vehicle for other medicaments, the compositions can contain up to 5% of such ingredient, the concentration being determined with reference to the particular ingredient.

It is desirable that a surfactant be included with the addition of therapeutic ingredients and in the same concentrations as the therapeutic ingredients. Polysorbate 80 is the preferred surfactant.

The ointment compositions are easily prepared by simply melting all the ingredients together. The preferred procedure is to melt the ingredient with the highest melting point first and then add the other ingredients in the order of decreasing melting points with the fluid ingredients added last. The melt is then stirred, strained and allowed to cool.

The water-in-oil compositions are prepared by first preparing the ointment, keeping it in the melted state, stirring in the water which is heated to the same temperature as the melt, and stirring until cool. Alternatively the water can be incorporated with the already prepared ointment by means of a tile and spatula. The glycerin, anti-oxidant, and preservative can be dissolved in the water prior to the addition of the water to the ointment.

The oil-in-water compositions are prepared following the usual procedure for the preparation of emulsions. As is usual in the preparation of emulsions, due care is given with regard to temperature, speed of mixing or additions, and the pressure of the homogenizer.

In preparing the oil-in-water emulsions, the oleaginous ingredients are melted together in the manner for preparing the ointment forms. The temperature should be higher than the melting point to maintain the mixture in a fluid condition, a temperature of from 150 to 180° F. is preferred. The oil is added slowly to water, with the water having a temperature within 10° of the oil. The addition is made slowly and with stirring to form the emulsion. The emulsion is then passed through a homogenizer heated to the temperature of the emulsion (about 150—160° F.). Excessive pressure, i.e., above 1500 p.s.i., is to be avoided and about 1000 p.s.i. is preferred. After passing through the homogenizer, the emulsion is cooled to room temperature with stirring.

When additional ingredients such as antioxidants, preservatives, therapeutic ingredients and the like are included in the ointments they can be stirred into the melt before cooling or added to the cooled ointment.

When adding such additional ingredients to the emulsions, the water soluble ingredients are dissolved in a portion of the water and added after the emulsion is formed and before homogenizing. The water insoluble ingredients, suitably comminuted are stirred into the emulsion before homogenizing.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1

One thousand grams of the composition are made from the following types and amounts of ingredients:

Cholesterol	50 gm.
Cetyl alcohol	60 gm.
Stearyl alcohol	60 gm.
Spermaceti	60 gm.
Stearic acid	100 gm.
Glyceryl monooleate	50 gm.
White petrolatum	80 gm.
Squalene	50 gm.
Corn oil	190 gm.
Oleic acid	200 gm.
Glyceryl monostearate	100 gm.

Melt all solids, add liquids, and heat until a clear solution results. Strain through cheesecloth and allow to cool at room temperature.

The composition so prepared is usefully applied to the human skin for treatment of the condition known as dry skin.

EXAMPLE 2

One thousand grams of the composition of the present invention are prepared from the following types and amounts of ingredients:

Stearic acid	100 gm.
Oleic acid	200 gm.
Glyceryl monooleate	50 gm.
Glyceryl monostearate	100 gm.
Corn oil	250 gm.
Spermaceti	20 gm.
Liquid petrolatum, viscosity 180	80 gm.
Squalene	50 gm.
Cholesterol	30 gm.
Cetyl alcohol	40 gm.
Stearyl alcohol	30 gm.
Lauryl alcohol	50 gm.

Melt all solid ingredients together, add the liquid ingredients, and heat until a clear solution results. Strain through cheesecloth and allow to cool at room temperature.

The composition so prepared is usefully applied to the human skin for treatment of the condition known as dry skin.

EXAMPLE 3

Four thousand cc. of the composition of the present invention are prepared from the following types and amounts of ingredients:

Composition of Example 2		1000 gm.
α-Tocopherol		0.9 gm.
Methylparaben		1.5 gm.
Propylparaben		0.9 gm.
Glycerin		200 gm.
Deionized water	q.s. ad	4000 cc.

The 1000 grams of the composition of Example 2 are melted and the tocopherol is added to the melt and the temperature adjusted to 180° F. The methylparaben, propylparaben, and glycerin are dissolved in 2000 cc. of water and heated to 200° F. The oleaginous melt is added to the heated aqueous solution and an emulsion is formed with continuous stirring. With continuous stirring, the emulsion is allowed to cool to 150° F. and passed through a homogenizer previously heated to 150° F., at moderate pressure (1000 p.s.i.). The remaining water at 150° F. is passed through the homogenizer as a wash and added to the emulsion. The emulsion is then stirred until it cools to room temperature.

The foregoing composition is an o/w lotion and is usefully applied to the human skin for the treatment of dry skin.

EXAMPLE 4

Three thousand grams of the composition of the present invention is prepared from the following types and amounts of ingredients:

Oleic acid	200.0 gm.
Stearic acid	100.0 gm.
Corn oil	250.0 gm.
Glyceryl monostearate	150.0 gm.
Spermaceti	20.0 gm.
Cholesterol	30.0 gm.
Cetyl alcohol	50.0 gm.
Stearyl alcohol	50.0 gm.
Lauryl alcohol	20.0 gm.
Mineral oil, viscosity 180	80.0 gm.
Squalene	50.0 gm.
α-Tocopherol	0.9 gm.
Methyl-p-hydroxybenzoate	1.5 gm.
Propyl-p-hydroxybenzoate	0.9 gm.
Glycerin	150 gm.
Deionized water q.s. ad	3000 gm.

The stearic acid, glyceryl monostearate, spermaceti, cholesterol, cetyl alcohol, and stearyl alcohol are melted together. The oleic acid, corn oil, lauryl alcohol, mineral oil, squalene, and tocopherol are added to the melt and the temperature adjusted to 180° F. The methyl-p-hydroxybenzoate, propyl-p-hydroxybenzoate and glycerin are dissolved in 1000 grams of water and heated to 200° F. The oleaginous melt is added to the heated aqueous solution and the emulsion is formed with continuous stirring. With continuous stirring, the emulsion is allowed to cool to 150° F. and passed through a homogenizer previously heated to 150° F., at moderate pressure (1000 p.s.i.). The remaining water at 150° F. is passed through the homogenizer as a wash and added to the emulsion. The emulsion is then stirred until it cools to room temperature. The foregoing composition is an o/w cream and is usefully applied to the human skin for the treatment of dry skin.

EXAMPLE 5

One thousand grams of the composition are made from the following types and amounts of ingredients:

Cholesterol	50 gm.
Cetyl alcohol	60 gm.
Stearyl alcohol	60 gm.
Spermaceti	60 gm.
Stearic acid	100 gm.
White petrolatum	70 gm.
Squalene	50 gm.
Expressed almond oil	250 gm.
Oleic acid	200 gm.
Glyceryl monostearate	100 gm.

Melt all solids, add liquids, and heat until a clear solution results. Strain through cheesecloth and allow to cool at room temperature.

The composition so prepared is usefully applied to the human skin for treatment of the condition known as dry skin or prophylactically for the prevention of dry skin.

EXAMPLE 6

One thousand grams of the composition are made from the following types and amounts of ingredients:

Cholesterol	30 gm.
Cetyl alcohol	60 gm.
Stearyl alcohol	60 gm.
Spermaceti	60 gm.
Stearic acid	100 gm.
White petrolatum	80 gm.
Squalene	60 gm.
Cottonseed oil	150 gm.
Oleic acid	200 gm.
Glyceryl monostearate	200 gm.

Melt all solids, add liquids, and heat until a clear solution results. Strain through cheesecloth and allow to cool at room temperature. The composition so prepared is usefully applied to the human skin for treatment of the condition known as dry skin. It is also highly useful as a vehicle for topical cosmetic and medicinal purposes.

EXAMPLE 7

Forty-five hundred cc. of the composition of the present invention are made from the following types and amounts of ingredients:

Polysorbate 80	90 gm.
Cholesterol	30 gm.
Cetyl alcohol	40 gm.
Stearyl alcohol	30 gm.
Spermaceti	20 gm.
Stearic acid	100 gm.
Glyceryl monostearate	100 gm.
Glyceryl monooleate	50 gm.
Mineral oil, viscosity 180	80 gm.
Squalene	50 gm.
Corn oil	250 gm.
Oleic acid	200 gm.
α-Tocopherol	0.225 gm.
Glycerin	225 gm.
Methylparaben	9 gm.
n-Butyl-p-hydroxybenzoate	13.9 gm.
Lauryl alcohol	50 gm.
Hydrocortisone acetate	45 gm.
Neomycin sulphate	25.2 gm.
Deionized water q.s. ad	4500 cc.

The cholesterol, cetyl alcohol, stearyl alcohol, spermaceti, stearic acid, and glyceryl monostearate are melted together. The glyceryl monooleate, mineral oil, squalene, corn oil, oleic acid, lauryl alcohol, n-butyl-p-hydroxybenzoate and tocopherol are added to the melt and the mixture heated to 160° F. Seventy grams of polysorbate 80, and methylparaben, and glycerin are added to 1500 cc. of water and heated to 160° F. The oleaginous melt is strained into the water and stirred until emulsified. The neomycin sulphate is dissolved in 100 cc. of water, filtered, heated to 160° F. and stirred into the emulsion. A slurry is prepared of the hydrocortisone acetate, the remaining 20 grams of polysorbate 80 and 100 cc. of water by passing through an homogenizer. The slurry is heated to 160° F. and stirred into the emulsion. The emulsion is then passed through the homogenizer and sufficient water added to make 4500 cc.

The composition so prepared is a lotion useful in the treatment of skin diseases where hydrocortisone and neomycin are indicated, such as in various forms of allergic dermatitis and other inflammatory skin diseases including contact dermatitis, neurodermatitis, topic dermatitis (allergis exzeme), seborrheic dermatitis, and the like.

EXAMPLE 8

Three thousand grams of the composition of the present invention are prepared from the following types and amounts of ingredients:

Polysorbate 80		60 gm.
Cholesterol		30 gm.
Cetyl alcohol		50 gm.
Stearyl alcohol		50 gm.
Spermaceti		20 gm.
Stearic acid		100 gm.
Glyceryl monostearate		150 gm.
Lauryl alcohol		20 gm.
Mineral oil, viscosity 180		83 gm.
Squalene		47 gm.
Corn oil		250 gm.
Oleic-acid		200 gm.
α-Tocopherol		0.15 gm.
Glycerin		150 gm.
Methylparaben		3 gm.
n-Butyl-p-hydroxybenzoate		12 gm.
Neomycin sulphate		17.2 gm.
Hydrocortisone acetate		30 gm.
Deionized water	q.s. ad	3000 gm.

The cholesterol, cetyl alcohol, steryl alcohol, spermaceti, stearic acid, and glyceryl monostearate are melted together. The lauryl alcohol, mineral oil, squalene, corn oil, oleic acid, tocopherol, and n-butyl-6-hydroxybenzoate are added and the oleaginous melt heated to 180° F. The glycerin, methylparaben, and polysorbate 80 are dissolved in 1000 grams of water at 180° F. The oleaginous melt is strained through cheesecloth into the solution and stirred to form an emulsion. The neomycin sulphate is dissolved in 50 grams of water at 180° F., filtered, and stirred into the emulsion. A slurry is prepared of the hydrocortisone acetate and 100 grams of water by passing through a homogenizer. The slurry is heated to 160° F. and stirred into the emulsion. The emulsion is stirred until it cools to 150° F. and then passed through a homogenizer. Sufficient water at 150° F. is added to make 3000 grams.

The composition so prepared is a cream useful in the treatment of skin diseases where hydrocortisone and neomycin are indicated as described in Example 5 above.

EXAMPLE 9

2000 cc. of the composition of the present invention are prepared from the following types and amounts of ingredients:

6α-methyl-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione	0.5 gm.
Polysorbate 80	20 gm.
Cholesterol	12 gm.
Cetyl alcohol	16 gm.
Stearyl alcohol	12 gm.
Spermaceti	8 gm.
Stearic acid	40 gm.
Glyceryl monostearate	40 gm.
Glyceryl monooleate	20 gm.
Oleyl alcohol	20 gm.
Mineral oil, viscosity 180	32 gm.
Squalene	20 gm.
Corn oil	100 gm.
Oleic acid	80 gm.
α-Tocopherol	1 gm.
Glycerin	100 gm.
Methylparaben	4 gm.
n-Butyl-p-hydroxybenzoate	6 gm.
Deionized water, q.s. ad	2000 cc.

The cholesterol, cetyl alcohol, stearyl alcohol, spermaceti, stearic acid, and glyceryl monostearate are melted together, the oleyl alcohol, glyceryl monooleate, mineral oil, squalene, corn oil, oleic acid, tocopherol, and n-butyl-p-hydroxybenzoate added, and the oleaginous melt heated to 180° F. The melt is strained through cheesecloth and stirred into a solution heated to 180° F. of the methylparaben and 800 cc. of water to form an emulsion. A slurry is prepared by passing the steroid, glycerin, polysorbate 80, and 200 cc. of water through a homogenizer. The emulsion is passed through the homogenizer and the slurry heated to 160° F. is stirred into the emulsion. Sufficient water at 160° F is added to the emulsion to make 2000 cc. and the emulsion is stirred until cooled to room temperature.

The composition so prepared is a lotion useful in the treatment of skin diseases where 6α - methyl - 9α - fluoro - 11β,17α - dihydroxy-1,4 - pregnadiene - 3,20 - dione, an anti-inflammatory agent, is indicated.

Following the procedure of the preceding example, a lotion is prepared having neomycin sulphate in addition to the above ingredients. 11.2 grams of neomycin sulphate dissolved in 200 cc. of water heated to 160° F. is added to the emulsion after the addition of the slurry.

Example 10

Two thousand grams of the composition of the present invention are prepared from the following types and amounts of ingredients:

6α-methyl-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione	0.5 gm.
Polysorbate 80, U.S.P.	20.0 gm.
Cholesterol	20.0 gm.
Cetyl alcohol	33.3 gm.
Stearyl alcohol	33.3 gm.
Spermaceti	13.3 gm.
Stearic acid	66.7 gm.
Glyceryl monostearate	100.0 gm.
Lauryl alcohol	13.3 gm.
Mineral oil, viscosity 180	53.3 gm.
Squalene	33.3 gm.
Corn oil	166.7 gm.
Oleic acid	133.3 gm.
α-Tocopherol	1.0 gm.
Glycerin	100.0 gm.
Methylparaben	4.0 gm.
n-Butyl-p-hydroxybenzoate	6.0 gm.
Deionized water, q.s. ad	2000.0 gm.

The cholesterol, cetyl alcohol, stearyl alcohol, spermaceti, stearic acid, and glyceryl monostearate are melted together, the glyceryl monooleate, oleyl alcohol, mineral oil, squalene, corn oil, oleic acid, tocopherol and n - butyl - p - hydroxybenzoate added, and the oleaginous melt heated to 180° F. The melt is strained through cheesecloth and stirred into a solution heated to 180° F. of the methylparaben and 800 cc. of water to form an emulsion. A slurry is prepared by passing the steroid, glycerin, polysorbate 80, and 200 cc. of water through a homogenizer. The emulsion is passed through the homogenizer and the slurry heated to 160° F. is stirred into the emulsion. Sufficient water at 160° F. is added to the emulsion to make 2000 grams and the composition stirred until cooled to room temperature.

The composition so prepared is a cream useful in the treatment of skin diseases where 6α - methyl - 9α - fluoro - 11β,17α - dihydroxy-1,4 - pregnadiene - 3,20 - dione, an anti-inflammatory agent, is indicated.

Following the procedure of the preceding example, a cream is prepared having neomycin sulphate in addition to the above ingredients. 11.2 grams of neomycin sulphate dissolved in 200 cc. of water heated to 160° F. is added to the emulsion after the addition of the slurry.

WHAT WE CLAIM IS:—

1. A dermatological composition for therapeutic treatment of the human skin comprising about 5% to 20% of saturated fatty acids having not less than 12 and not more than 20 carbon atoms, about 10% to 30% of unsaturated fatty acids having not less than

12 and not more than 20 carbon atoms, about 10% to 20% of glyceryl monostearate, about 15% to 25% of a fixed oil, about 2% to 10% of a wax consisting of esters of a fatty acid having not less than 12 and not more than 20 carbon atoms and a fatty alcohol having not less than 12 and not more than 20 carbon atoms, about 5% to 18% of a fatty alcohol having not less than 12 and not more than 20 carbon atoms, about 2% to 5% of cholesterol, about 3% to 8% of squalene, and about 5% to 15% of petrolatum, liquid petrolatum or mixtures thereof.

2. As a dermatological composition, an oil in-water emulsion comprising the composition of claim 1 dispersed in water in the proportions of 1 part of the composition of claim 1 to about 1 part to 19 parts of water.

3. The dermatological composition of claim 2 containing from about 0.01% to about 0.1% of a dermatologically acceptable antioxidant, from about 0.01 to about 0.05% of preservatives, and about 1 to 5% glycerin.

4. As a dermatological composition, a water-in-oil emulsion comprising about 1 to 15 parts of water dispersed in about 85 to 99 parts of the composition of claim 1.

5. A dermatological composition for therapeutic treatment of human skin comprising about 5% cholesterol, about 6% cetyl alcohol, about 6% stearyl alcohol, about 6% spermaceti, about 10% stearic acid, about 5% glyceryl monooleate, about 8% petrolatum, about 5% squalene, about 19% corn oil, about 20% oleic acid, and about 10% glyceryl monostearate.

6. A dermatological composition, an oil-in-water emulsion comprising 1 part of the composition of claim 5 dispersed in about 1 part to 19 parts of water.

7. The dermatological composition of claim 6 containing about 0.03% of α-tocopherol, about 0.1% of a preservative, and about 5% glycerin.

8. As a dermatological composition, a water-in-oil emulsion comprising about 1 to 15 parts of water dispersed in about 85 to 99 parts of the composition of claim 5.

9. A dermatological composition substantially as herein described with reference to any of the Examples.

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